REMARKS

Claims 1, 5, 10, 25 and 27- 29 have been amended. Claims 1-5, 8-10, 14-18, 21, 22, and 25-29 are currently pending in the application.

Amendments to the Specification

Again, as with the Amendments to the Specification, the text of this subsection has been revised, as requested by the Examiner, to contain correct paragraph references. Otherwise the content is the same as presented in the previous response and resubmitted response to the Office Action of April 14, 2004:

The specification has been amended to address concerns raised by the Examiner regarding numerical identifiers that appear in the figures, but which are not mentioned in the specification.

With respect to element 204 shown in Figures 4A and 4B, the specification has been amended to have label 204 refer solely to a microchannel, thereby relieving the objection raised by the Examiner.

The reference label 466 in paragraph [0096] has been removed.

With respect to element 511 in Figure 5, the specification has been amended to include reference to element 511.

With respect to elements 480 and 482 in Figure 6D, the specification has been amended to include reference to these elements.

With respect to elements 604 and 608 in Figure 8, the specification has been amended to include reference to these elements.

With respect to elements 100 and 101 in Figure 9, the specification has been amended to include reference to these elements.

With respect to elements 800 and 820 in Figure 18, the specification has been amended to include reference to these elements.

With respect to element 880 in Figure 22A, the specification has been amended to include reference to element 880.

With respect to Figure 12A, reference to this figure was inadvertently left out of the discussion in paragraph [00109], comparing the results illustrated in Figures 12A and 12B. The subject of this comparison is clearly stated in the Brief Description of the Drawings, in paragraphs [0024] and [0025]. By amendment to the specification a reference to Figure 12A is now included.

Basis for the amendments to the specification are summarized in the table:

Amendment	Basis
Para. [0078]	Para. [0091] provides the governing description.
Para. [0095]	Description of illustration of Figure 5.
Para. [0096]	Deleted reference to unlabeled component of the figure
Para. [0097]	Description of illustration of Figure 6D.
Page 29, para. [0099]	Description of illustration of Figure 8.
Page 29, para. [00100]	Description of illustration of Figure 9.
Page 31, para. [00109]	Paragraph [0024].
Page 38, para. [00142]	Description of illustration of Figure 18.
Page 39, para. [00146]	Typographic correction.
Page 40, para. [00148]	Description of illustration of Figure22A.

Amendments to the Claims

Among the pending claims, claims 5, 10, 28 and 29 have been amended to render the claims 'definite'. Applicants assert that the basis for the amendments to the claims are clear from the context. Please see the section below "Rejections under 35 U.S.C. § 112" for a full discussion.

The remaining claim amendments have been made to distinctly include operating parameters of the subject invention that produce the advantages gained by reduction of bubble formation at electrodes in fluidic devices. Basis for the new claims are as follows:

Claim	Term/Phrase	Basis
1	operations at high field strengths	Paragraph [00113] compares the results of high field strength operation when using either platinum, carbon or silver/silver chloride electrodes. The results establish the utility of silver/silver chloride electrodes at field strengths higher than those where Pt electrodes are effective This is the basis for the comparative language of claim 25 previously presented, qualifying the usage of silver/silver chloride for high field strength operations as fields at which Pt electrodes are disadvantageous because they would produce bubbles. Paragraph [00128] demonstrates the successful efforts to futher extend the operable high field strength range in a microfluidice device over that which can be achieved with Pt electrodes.
1	to apply a field of at least 400 V/cm	Paragraph [00126], line 4.
25	establishing a field of at least 400 V/cm	Paragraph [00126], line 4.

27	at least one of said electrodes	equivalent to the original language: "an electrode" but more precise

No new matter has been added by the amendments. Reconsideration of the application is respectfully requested.

The Invention

The invention provides devices and methods for reducing the amount of bubbles formed at an electrode that would otherwise interfere with the operation of a fluidic device in high potential, electrokinetic applications. This is particularly an issue when the fluidic device is comprised of chambers, reservoirs or channels having small (micron- to hundreds of micron-sized) features or openings (see paragraph [0053]). Even if the bubbles do not themselves block the openings completely and cause a loss of electrical conductivity within the fluidic system, a changing population of bubbles was noted to adversely impact the performance of the device for these applications, probably because the bubbles caused the electric field strength to vary.

Early results in the field of microfluidics generally showed variability, and although reproducibility was acceptable, means to overcome problems associated with bubbles and gas/liquid interfaces were desired. This was one of the key challenges of the field, as noted in Nature Biotechnology, 2001, Vol 19(8), p. 717. (Article is attached). Thus, although there was a long felt need in the field for such improvements, none were forthcoming. The question was how to engineer a device to provide large potentials and large currents within the confining space of a microfluidic device?

To reiterate what was said in the previous response, to Applicant's knowledge, all commercially available instruments for capillary electrophoresis, gel electrophoresis and the like are made with metal electrodes, generally platinum. (See, for example systems from Invitrogen, Owl Separation Systems, Applied Biosystems, Amersham, etc. and a general discussion in "Introduction to Capillary Electrophoresis found at http://www.anamap.co.uk/pdf/ce_intro.pdf, article is attached). However, bubble generation is vigorous at noble metal electrodes and clearly problematic for small devices.

A typical approach to solving such a problem might have been to employ an electrode material that exhibits a large overpotential for the expected electrolysis reactions, e.g. one at which

water is not readily reduced or oxidized. Carbon electrodes are a good candidate material, and one which was tested by inventors, as is disclosed in the application. Silver/silver chloride electrodes were not initially expected to solve the problem because they are typically used as either a reference electrode or as a counter electrode in low voltage/low current applications (including low voltage electrophoretic applications). However, surprisingly, silver/silver chloride-based electrodes were found (1) to be useful as a driving electrode in a high voltage application, and furthermore found (2) to surpass the performance of carbon electrodes in the suppression of bubble formation.

The finding that silver/silver chloride electrodes could be used in a high voltage application, as a driving electrode in an electrokinetic device, was unexpected. Futhermore, suppression of bubble formation better than any other material tested, was also unexpected.

Rejections Under 35 U.S.C. § 112

The Examiner rejected claims 5, 10, 28 and 29 under 35 U.S.C. §112, second paragraph as being indefinite for failing to distinctly claim the subject matter. Applicants respectfully disagree with this rejection, particularly in view of the amendments.

Claims 5 and 10 have been amended to recite the alternative expression according to the language of *Ex parte Markush*, 1925 C.D. 126. Claims 28 and 29 have been amended such as to provide proper antecedent basis for the term "the ink".

In view of these amendments, Applicants respectfully request that the above rejection be withdrawn.

Rejections Under 35 U.S.C. 103

The Examiner rejected claims 1-5, 8-10,14-18, 21, 22 and 25-29 as being unpatentable over U.S. Patent 6,375,871 to Bentsen et al. in view of Guy et al (U.S. Patent 5,362,307) and Chan (U.S. Patent 5,565,143). Bentsen discloses some features of the subject claims, such as a cover, a substrate, a fluid reservoir, a microchannel and a conductive circuit trace, and assembles them in a microfluidic device, but provides no specific disclosure of silver/silver chloride inks or materials. Guy teaches silver/silver chloride electrodes for low voltage applications (Col. 6, lines 57-59) and Chan discloses compositions useful for one of several ways to prepare such electrodes on various substrates, including plastic dielectric films (Col. 2, lines 35-37). Lastly, the Examiner holds the position that bubble formation would inherently be reduced in a device of Bentsen et al, when the above teachings are combined and a silver/silver chloride electrode is used.

Applicants respectfully disagree with this rejection for the reasons stated below, particularly in view of the above amendments to the pending claims.

Before addressing the question of the 'inherency' of the properties of the electrode material and the attendant functional performance that is observed, Applicants respectfully rebut the establishment of a prima facie case of obviousness based on the combination of references. The first of the three necessary criteria to establish obviousness is that there must be either a suggestion or motivation in the reference or in the general knowledge of skilled artisan to combine the references. The fact that the teachings of two or more references can be combined does not mean that the combination is obvious absent the suggestion or motive to combine them.

Applicants assert that there was neither a suggestion nor a motivation to combine the cited references in the manner suggested. In Chan, the objective is to provide an environmentally sound, and perhaps more cost-effective method for fabricating silver/silver chloride electrodes on plastic substrates. (Col. 2, lines 12-16). Use of these electrodes at high voltages is neither contemplated, suggested, nor addressed in any way. The applications suggested by Chan, including EKG monitor (Col. 1, line 14), reference electrode (Col. 1, line 25) and biosensor (Col. 1, line 26), are appropriate because the electrode can deliver a "continuous current at a low and steady voltage" (Col. 1, lines 22-23), but do no more than affirm the known properties of these electrodes. Chan does note the use of these electrodes for electrophoresis, but only in cases where a "*low* and steady voltage" is required (Col. 1, line 23, emphasis added). Nowhere does Chan indicate that silver/silver chloride electrodes might be useful for applying high voltages in microfluidic devices.

Guy discloses the use of silver/silver chloride electrodes, chosen for their non-polarizability (Col. 20, line 17), a property also noted by Chan (Col. 1, line 15). As with Chan, Guy discloses only low voltage applications of silver/silver chloride electrodes. It must be noted that the devices of Guy are operated at no more than 15 V, and "preferably between about 1 and 10 volts, and especially at about 5 volts" for all disclosed applications (Col. 6, lines 57-59). Thus, the disclosures of Guy are equivalent to the disclosures of Chan: silver/silver chloride electrodes are useful for delivering steady performance at low bias potentials. Here again there is no indication such electrodes might be useful for applying high voltages in devices.

Using the disclosure of Bentsen as a starting point for preparing a microfluidic device for biological applications, one would be lead to any of the several suggested conductive materials, "electrically conductive traces (e.g. traces made from nickel, gold, platinum, palladium, copper, conductive silver-filled inks, or conductive carbon-filled inks)" (Column 11, lines 1-4) for forming microelectronic elements (i.e. electrodes). The disclosure however provides no discussion or

motiviations for choosing one material over another in fabricating an electrode. There is no indication that any one material might be preferred over another, whether it be for ease of manufacture, stability or compatibility with any intended use. Specifically, there is no recognition of the need for bubble reduction in electrokinetic applications.

A silver/silver chloride electrode, as noted above, is functionally different from the metal electrodes listed by Bentsen and thus would not be expected to be used interchangeably. Bentsen does not suggest, for any functional or performance-related reason, the use of any other electrode material beyond those taught in the disclosure. Thus, Bentsen would not lead an interested party to search for the disclosures of Guy or Chan. Applicants maintain that neither Chan, Guy nor Bentsen provides motivation or suggestion to use silver/silver chloride electrodes in microfluidic devices, or indicate the desireability of the subject invention. In contrast, Applicants have expressly taught the functional performance differences among various electrode types, and highlight the advantage of using silver/silver chloride electrodes in high voltage operations in microfluidic devices.

Even if the reason for combining references (which was not made explicit in the references as argued above) was made by the skilled artisan we come to the same conclusion. Again starting from Bentsen, one might seek the teachings of Guy or Chan for the use of silver/silver chloride electrodes, but the only guidance gained would be that such electrodes might be more safely produced, or might be more cost effective, or might serve usefully for low voltage applications. Thus no expectation for the claimed, subject invention would be gained by a skilled artisan looking at these references. Moreover, there is no clear benefit to be gained by combining the various references beyond what could already be achieved based on the teachings of Bentsen alone. The materials disclosed in Bentsen provide the same possible advantages as those touted in Guy or Chan.

Without the appearance of a suggestion or motivation to combine the cited references, Applicants assert that a prima facie case for an obviousness rejection cannot be maintained.

Furthermore, Applicants submit that whether or not the reduced amount of bubbles generated at a silver/silver chloride electrode is an inherent property (the amount of bubbles generated will depend considerably on at least temperature, solvent, electrolyte and analyte composition, current density, electrode morphology and geometry), this question should not be reached because the claimed invention is not directed to the same processes or methods of the references.

New uses of known processes or methods are patentable by statute, 35 U.S.C. § 101. The claimed process of the subject invention is for a new use that is distinct from any of the uses described by the cited references. While the Federal Circuit noted in Bristol-Meyers Squibb Co. v. Ben Venue Labs, Inc., 58 USPQ2d 1508 at 1514, that "newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent", they prefaced this by stating that the converse did hold: known processes directed to a new purpose may be patented.

The principles of inherency largely hold when a prior art device, in its normal and usual operation, would perform the claimed method. In MEHL/Biophile International Corp. v. Milgraum, 192 F.3d 1362, 1366, one critical factor in the determination that the objective of the patent, hair depilation by laser, was inherent in a prior art reference was the fact that "the laser operating parameters . . . substantially coincide with those disclosed in the patent. Accordingly, to the extent the embodiment in the patent achieves hair depilation so does the [prior art] method." The ruling illustrates that inherency may be found in a *method* claim where the effect is achieved within the same operating parameters as the prior art disclosure. In Titanium Metals Corp v. Banner, 778 F.2d 775, 776, the court held that the claim to an alloy "characterized by good corrosion resistance" was anticipated by a prior art reference that disclosed an alloy containing the same recited components. The ruling here illustrates that a *composition of matter* claim to a new property (i.e. corrosion resistance) was invalid because it was inherent in the prior art disclosure of the very same material.

A distinction should be drawn between the method claims of the subject invention and the various methods suggested in the prior art: there is no overlap between the normal use and operation of microfluidic devices as suggested and motivated by the prior art references (were one to combine them) as described earlier and that of the subject invention. The subject invention recites a method that is beyond what could reasonably be said to have been anticipated by the prior art. Accordingly, because the subject invention requires operation in regimes of current and voltage beyond those described in the prior art references, Applicants assert that the advantages claimed in the subject invention are not 'inherent'. The materials and methods herein are not directed to the same purposes previously described but are directed to a new purpose and thus may be patented.

In view of the above, and the amendments to the claims introducing the limitation of high potential fields at silver/silver chloride electrodes, Applicants respectfully request that the rejection under Bentsen in view of Chan and Guy be withdrawn.

The Examiner also separately rejected claims 1-5, 8-10, 14-18, 21, 22, and 25-29 as being unpatentable over U.S. Patent 6,103,199 to Bjornson et al ("Bjornson '199")., U.S. Patent 6,623,860 to Hu et al ("Hu '860"), U.S. Patent 6,284,113 to Bjornson et al. ("Bjornson '113") and U.S. Patent Application Publication No. 2002/0092767 to Bjornson et al. ("Bjornson '767"), respectively, each in view of Guy et al (U.S. Patent 5,362,307) and Chan (U.S. Patent 5,565,143). In each case, the Examiner argued that the primary reference teaches the claimed microfluidic device wherein the electrodes can be prepared from, e.g. conductive ink, and then again cited Guy for disclosing the use of silver/silver chloride traces as driving electrodes and Chan for teaching an improved method for silver/silver chloride electrode fabrication. The Examiner asserted that bubble formation would be inherently reduced when silver/silver chloride electrodes are used in any of these devices.

Applicants respectfully disagree for essentially the same reasons stated above for Bentsen, and in view of the above amendments. None of the references suggest using silver/silver chloride under the conditions of Applicants' invention, nor does any disclosure provide motivation for choosing any one of materials disclosed over any another in fabricating an electrode due to some consideration for the functional need of an intended application, such as Applicants' high voltage application. Thus, again Applicants assert there is no motivation or suggestion to combine any of the primary references with either Chan or Guy.

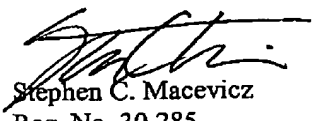
Moreover, even if any of Bjornson '199, Hu '860, Bjornson '113, or Bjornson '767 could be combined with Guy or Chan, the rejection thereunder would still be untenable because each of these cited references and the present application were, at the time the invention was made, owned by, or subject to an obligation of assignment to, the same person, namely, ACLARA Biosciences, Inc. Therefore, they are not qualified art under 35 U.S.C. 103(c).

Accordingly, Applicants respectfully request that the above rejection be withdrawn.

For the above reasons, Applicants submit that any basis for rejection has been overcome by amendment or argument and respectfully request that all rejections be withdrawn, and that the claims be allowed and the application quickly passed to issue.

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account **50-2266.**

Respectfully submitted,



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